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Southwestern MEDICINE

OFFICIAL JOURNAL OF THE SOUTHWESTERN MEDICAL ASSOCIATION AND EL PASO COUNTY MEDICAL SOCIETY

August, 1950

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"A SENSELESS ACT FOR WHICH NO ADEQUATE EXPLANATION IS POSSIBLE"

On December 4, 1949, the records of the Hillsborough County General Hospital, Goffstown, New Hampshire, show that Dr. Hermann N. Sander injected air into a vein of one Abbie Borroto, his patient. Now the press announces that Dr. Sander has been reinstated by the New Hampshire Board of Registration of Medicine so that he may again practice his profession. This particular case has been widely publicized. It has brought unfortunate assumptions as regards the profession in general. It has given rise to destructive criticism. Naturally the lay press has highly publicized the proceedings in general.

It is news, and we must accept the fact that the press is entirely within its right to give this whatever publicity they may feel it deserves. This act of Dr. Sander has been instrumental in gaining membership for the Euthanasia Society of the United States. The Euthanasia Society is made up of both physicians and lay members. Its membership has never been large, and even with this episode, in all probability, its membership is still under 600. When one considers that this society has only about one hundred members of the profession listed, it would seem that Euthanasia. lacks popularity with the profession as a whole.

REPORT QUOTED

In order that the Readers of SOUTHWESTERN MEDICINE be fully acquainted with the action insofar as the profession itself is concerned, the report of the New Hampshire Board of Registration in Medicine, April 19, 1950, is herewith quoted:

> "The records of the Hillsborough County General Hospital, Goffstown, New Hampshire, indicate that on December 4, 1949, Dr. Hermann N. Sander injected air into a vein of one Abbie Borroto, his patient. At a hearing conducted by this Board on April 12, 1950, Dr. Sander admitted that he attempted to inject air into a vein of the aforementioned patient and that he did in fact inject air into that patient's body, although he now does not positively state whether or not he did in fact penetrate a vein. Dr. Sander stated to this Board that he thought the patient was dead when he injected the air. He was unable to offer any reason for injecting air into this patient. At the hearing his counsel stated that the injection of air by Dr. Sander was: **"a senseless act for which no adequate explanation is possible."** Dr. Sander further asserted that just prior to the air injections his mind **"snapped"** thereby precluding any explanation for his action.
>
> ### SANDER'S CONTENTION
>
> Dr. Sander contends that he has done no wrong by injecting air since he is certain that he did not kill his patient. This Board does not concern itself with the question of whether Dr. Sander's patient was alive or dead, but we cannot agree that he has done no wrong. It is common medical knowledge that the injection of air into the vein of a human body can serve no useful purpose and customarily every precaution is taken to avoid the introduction of air into a human vein. It is likewise clear that a physician's moral obligation to his patients and to his profession is to engage only in medical practices which are designed to cure or to alleviate disease. Any act of a physician which is not so designed fails to meet the moral standards of the medical profession. We can only conclude that when Dr. Sander deliberately injected air into his patient, he was either unable to recognize his moral obligation as a physician, or that he was willing to disregard that obligation. Under either view, his action is morally reprehensible according to medical standards. Obviously, no physician, whatever his professional standing, can be allowed to perform **"a senseless act for which no adequate explanation is possible."** In the unanimous opinion of this Board the action of Dr. Hermann N. Sander, here under consideration, indicates that he failed to meet the requirements of morality imposed upon him by his profession and by law. This Board finds that his "moral character" as we understand that term to be used in Revised Laws, chapter 250, section 14, is such as to require the revocation of his license under that law. Accordingly, his license to practice medicine in the State of New Hampshire is hereby revoked as of this date, April 19, 1950.
>
> No application of Dr. Sander for reinstatement by this Board will be entertained prior to June 19, 1950."

PROFESSIONAL OBLIGATION

It seems apparent that Dr. Sander was unable to comprehend the obligation which a physician owes, not only to his patients, but to the other members of the profession. It is all very well to explain that at the time this act was committed, the mind "snapped". It is a convenient explanation, but this cannot help to explain the situation clearly enough to allay doubts in the minds of the public or many members of the medical profession. It well may be that members of the Euthanasia Society, such as W. Somerset Maugham, Robert E. Sherwood, Eugene O'Neill; professional liberals, such as Arthur Garfield Hays, and Max Eastman; the birth controller, Margaret Sanger; and Reverend Harry Emerson Fosdick can well understand Dr. Sander's act which seemed nonsensical.

RANK AND FILE

However, the rank and file of the medical profession who are concerned with the suffering and the heartaches of individuals afflicted with illness and pain will find it extremely difficult to condone his action. It may be that some of us have not perhaps the intellect to understand this philosophy, but most of us are well satisfied to follow the ethics of the profession as they have been taught us for many years by our predecessors. It is sincerely hoped that now, since Dr. Sander is again in the act of practicing medicine, that he will not forget that he owes the medical profession in general a debt and that only his maintenance of the high standards of conduct expected of every physician can adequately pay this debt.

School Bus Safety

Illinois, Oregon, and several other states require Red Cross first aid training for school bus drivers. In Illinois alone, more than 50 Red Cross chapters conducted such training in the 1948-49 school year.

De Rebus Medicis Et Politicis

BY ROBERT B. HOMAN, JR., M. D., EL PASO, TEXAS
MEMBER OF THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION

THE HOUSE OF DELEGATES AT SAN FRANCISCO

The complete transactions of the House of Delegates of the American Medical Association will be printed in the Journal of the American Medical Association. It is, of course, impossible and unnecessary to attempt to present all of the transactions in brief in this short space. Over eighty separate resolutions and reports of councils and committees were deliberated by the House. Some of the actions of vital interest to all doctors will be reported and discussed here.

A very strong report in opposition to the practice of Medicine by hospitals was adopted. There was prolonged discussion of this matter both before the reference committee and from the floor of the House. The exploitation of doctors by hospitals is to be deplored. Anesthetists, pathologists and roentgenologists are particularly exploited in certain Eastern areas. The practice is spreading into the medical and surgical fields. Fortunately in our southwest the physician-hospital relationship, generally, remains ethical and mutually agreeable. It will remain so if the recommendations as adopted are followed. Hospital administrators and trustees and all physicians will find these recommendations important reading.

STRONG RESOLUTION

The House adopted a strong resolution in opposition to Reorganization Plan No. 27, and instructed the Officers and Trustees to enter into active opposition to the plan in Washington and elsewhere. On July 10, 1950, the House of Representatives vetoed Plan No. 27 by vote of 249 to 71. This is another victory for American Medicine over the socialist planners.

The highly successful National Education Campaign of the A. M. A. received the endorsement of your House of Delegates. In October 1950, just prior to congressional elections, a nation-wide advertising program will be inaugurated — using newspapers, radio and national magazines. Every bona-fide daily or weekly newspaper in the United States, Hawaii and Alaska (approximately 11,000 in number) will carry the A. M. A. ads. Thirty national magazines and some twenty advertising trade publications will also be used. An intensive "spot announcement" campaign will utilize time on over 300 radio stations covering every state.

IMPORTANT PROVISION

The purpose of the campaign is two-fold: First, to aid in every way possible in increasing the availability of good medical care to the American people through the medium of Voluntary Health Insurance. Second, American Medicine is determined to alert the American people to the danger of socialized medicine and to the threatening trend toward State Socialism in this country.

Beginning January 1, 1951, each dues paying member of the A. M. A. will receive the Journal of the American Medical Association. This important provision was initiated by the House of Delegates of the State Medical Association of Texas and was carried through to adoption by the Texas Delegates. Membership dues were again set at $25.00 for 1951 — subscription to J. A. M. A. to be included. Non-members subscription to the Journal was increased from $12.00 to $15.00. Fellowship dues, formerly $12.00, will be cut to not more than $5.00 and will be set at $2.00 at the interim session at Cleveland in December 1950. Thus, combined Membership and Fellowship dues, previously $37.00 will be $27.00 in 1951. Doctors who have not paid their $25.00 Membership dues for 1950 become delinquent in January 1951 and must remove this indebtedness or drop from the membership rolls February 1, 1951.

CONVENTION HIGHLIGHT

The highlight of the convention was the address of the incoming President, Dr. Elmer L. Henderson. For the first time in history, the inauguration ceremonies were broadcast to the doctors and the people of America. The strong, fighting address of Dr. Henderson left no one confused as to the position of American Medicine in the fight for Freedom in this country. That the socialization of Medicine is but the first step toward the complete socialization of all America is now becoming well known to Americans.

The necessity for all American doctors who believe in medical, economic and spiritual freedom to cooperate with the American Medical Association is obvious. The A. M. A. is over one hundred years old. It is fighting your fight as the respected leader of American Medicine. Your membership is of vital importance. No other medical association has the strength, authority, or leadership to halt the economic planners in their drive toward Socialism.

NEW MEXICO CANCER CONFERENCE

The annual New Mexico Cancer Conference will be held in Santa Fe, Oct. 27 and 28, at the La Fonda Hotel.

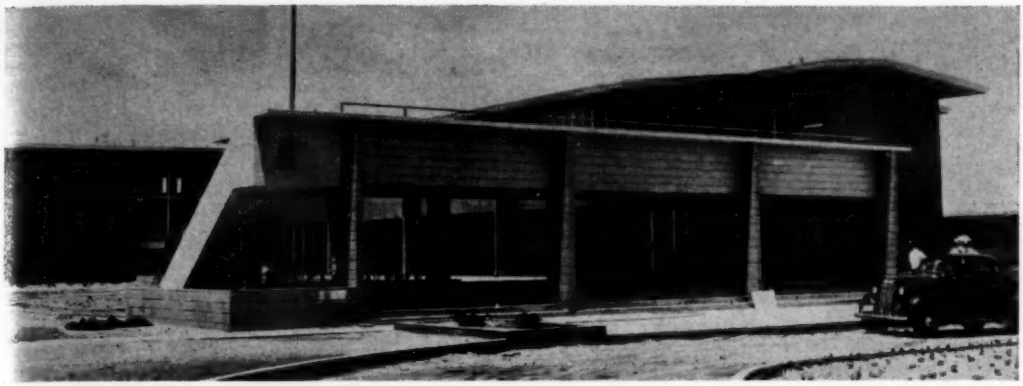
This meeting for the medical profession of the Southwestern states will have six eminent speakers from various parts of the United States.

The sponsors of the meeting are the American Cancer Society, the New Mexico Medical Society, and the Santa Fe County Medical Society.

Cancer Tests for Medical Students

During the past year 8,994 medical students in 32 schools were given a comprehensive "cancer test," consisting of 180 questions on precancerous lesions, diagnosis, metastases, treatment and prognosis. Object was to find weak spots in cancer teaching. Plenty were found. Although no significant regional differences were observed in the average scores, many schools obviously are bearing down on cancer much harder than are others. Wide variations existed between the average grades of senior students in different schools. Highest score was 150 out of a possible 180, or 83%; the winnah, a senior at University of Minnesota, is the son of a country M.D. Highest score by any medical school professor was 166; but this prof helped write the test. Huh!

THE LEA COUNTY COMMUNITY HOSPITAL



Lea County Community Hospital

In 1946, when the citizens of Lea County, New Mexico, found that their seventeen year experience of varying economic fortune had settled into a steady rise toward permanency and stability, they laid out a program of community enterprise designed to make it possible for the County to take care of its own needs in every way. Housing, schools, roads, new business construction, entertainment facilities were added or begun as soon as possible after the war's end. The entire complexion of the County, as well as its economic thinking, underwent a change.

High on the list of sorely needed facilities was a hospital, Lea County having had only a few small, privately owned, institutions theretofore. The County Commission determined to build not only for the present need, but for the future. Plans were made and discussed and presented to the people of the County repeatedly. All the citizens interested in the project were heard. The Lea County Medical Society was consulted. Outside medical and hospital experts were called in and gave their aid. The question was submitted to the voters, who overwhemingly approved a $750,000 bond issue for the purpose of constructing and equipping a County community hospital.

U. S. PARTICIPATES

Under the provisions of the Hill-Burton Act (Public Law 725), the Federal Government participated in the building cost to the extent of $200,000. Transfer of unused County funds was made by the Commissioners to the Hospital Fund, and the site of the hospital was donated by a group of citizens, bringing the total amount available to the Building Committee to $1,035,000.00.

Upon this basis, architects were called into consultation and actual plans and designs studied. W. L. Pereira, A.I.A., and Associates, of Los Angeles, were selected as the designers; Truman Mathews, A.I.A., of Santa Fe, the architect; and Davis and Foster, El Paso, as consulting engineers. Bids for the construction were taken, and the B. M. F. P. Construction Company, of Lubbock, was awarded the contract. Actual construction was begun in January, 1949.

DESIGN CHOSEN

The design settled upon, basically, is one embodying wide separation of patient rooms in wings, radiating from a core of service and diagnostic facilities. One of the wings has two stories, and there is a full basement which is used for cooking, storage, power plants and personnel cafeteria. Additional wings can be built, and the number of available beds increased, at any time without disturbing the function of the hospital or having to add service and diagnostic facilities.

The three principal patient wings house, respectively, surgical, obstetrical, and medical cases. A truncated, separate wing on the second floor will contain isolation rooms for infectious and contagious diseases. It will be possible to care for cases of poliomyelitis in the hospital, instead of sending patients with this disease away from home for treatment and care as has been done up to the present. Large nurseries will house the newborn infants, who may be seen both from within the nursery corridor as is usual in hospitals and from a gallery outside the building, thus making it possible for younger visitors (who may not be admitted to the maternity department) to see their newly born brothers and sisters in safety.

OPERATING ROOMS

Six operating rooms each designed for a specific purpose, will provide ample surgical facilities for the County. Two delivery rooms, and two labor rooms, which are located beside a private court in which mothers may sun themselves, are separated from the remainder of the hospital, in accordance with the principles of good hospital design, as is the maternity wing.

It is of interest that, although only the finest and most modern equipment has been bought for the Lea County Community Hospital, the total cost per bed for the hospital is only $12,937.50, fully equipped. This figure, when compared to the national $16,000 average for hospitals similarly equipped, indicates that Lea County is getting good value for its money, and that the long and careful preliminary studies paid off.

There are four separate heating and air conditioning systems; one for the hospital proper, one for the operating rooms, a third for the delivery rooms and nurseries, and the fourth for the kitchens and cafeteria. This will prevent reflux of used air, and will eliminate the distribution of cooking or other odors about the building.

COUNTY PRIDE

Lea County looks to its new Community Hospital with pride and enthusiasm. While it can never be a pleasure to be ill, it will at least be more comfortable than is usual to be a patient in the new institution. Lavish use of color (there are six basic color schemes for the patient's rooms alone), elimination of clinic-

railway station waiting room elements, and consideration of the patient's needs all point to a new kind of hospitalization for Lea County citizens. These people have planned, built, equipped, and paid for their hospital.

The hospital contains the following facilities: 80 adult beds; 26 bassinets; 4 infant incubators; 10 cribs for children aged 2 to 10 years; 8 isolation beds; 200 MA diagnostic x-ray; mobile x-ray; full clinical laboratory; public health clinic offices and rooms; electrocardiography and basal metabolism department; pharmacy; central sterilizing and supply department. Adult beds are divided into 22 private rooms each with a connecting toilet; 25 two-bed rooms; 2 four-bed rooms. The children's cribs are in a large ward, separated by glass partitions; the ward has a walled, private play yard for the children.

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Lay Education Materials

Patients should find in every physician's waiting room copies of the vest pocket size pamphlets published by the National Cancer Institute and American Cancer Society. Titles include *Cancer, What to Know, What to Do About It; Cancer of the Breast; Cancer of the Female Reproductive Organs; Cancer of the Digestive Tract; Cancer of the Mouth and Respiratory Tract; Cancer of the Genito-Urinary Tract;* and *Cancer of the Skin.* Sample copies may be obtained by writing to Cancer Reports Section, National Cancer Institute, Bethesda 14, Md. In bulk orders the cost is from $1.50 to $5.50 per 100, and are worth every penny.

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CHEMOTHERAPY OF NEOPLASTIC AND ALLIED DISEASES

By W. F. Bethard, M. D.* and L. O. Jacobson, M. D.**
University of Chicago***

EDITORIAL COMMENT: *This paper was presented early in 1949. The authors, since this time, have done considerable amount of investigation with "ACTH" and related compounds. There was some question in their minds as to the advisability of publication of this discussion without mention of this particular phase of their investigations. The Editorial Board of* SOUTHWESTERN MEDICINE, *however, is of the opinion that its readers should have the benefit of the authors' study of this particular problem, and fully realizes that these new developments in this field are of major importance. At the present time these developments are, literally, in their infancy, and it is felt that this paper is complete unto itself. In this connection, very recently, the Editor had an opportunity of attending a clinic conducted by a nationally known hematologist. In discussing a case of particularly resistant blood dyscrasia, he said "everything known has been tried, so what are we to do." Then, rather facetiously, he said, "ACTH."*

INTRODUCTION

Successful chemical therapeusis of malignant disease has been the ambition of medicine for nearly as long as such diseases have been recognized. Medical alchemy, in the form of exotic potions presaged modern treatment. Discovery of artificial radioactivity by Joliot and Curie in 1934 re-energized the flagging search. Inhibition or destruction of malignant cells by means of parenterally or orally administered radioactive elements was an intriguing idea. Clinical evidence that neoplasia with metastasis could be selectively inhibited by chemical means was shown by Huggins in 1941. Since that time, tremendous impetus in this field has been provided by developments in atomic energy and radio-chemistry which accompanied World War II. The following are a few of the agents, both radioactive and chemical, which have been proposed and evaluated in the treatment of neoplastic diseases.

RADIOPHOSPHOROUS (P^{32})

Radioactive phosphorous was first introduced into the treatment of leukemia by Lawrence, Scott, and Tuttle[1] in 1939. Known radiosensitivity of these tumors suggested that "chemo-radiation" would be of value. Theoretically, tissues utilize phosphorous proportionately to their rates of growth. Thus the more rapidly growing malignant cells "take up" more than normal cells, hence should receive the majority of radiation when such phosphorous is radioactive. This is based on the apparently valid assumption that radioactive isotopes of phosphorous possess chemical properties identical to those of the stable element. Tissue analyses by tracer techniques have shown that, although phosphorous is essential to the metabolism of every type of cell, it is preferentially concentrated in the reticulo-endothelial system.[2] Up-take ratios of tumor tissues are variable and correspond roughly to the efficacy of P^{32} therapy in the type of tumor considered.

CARRIER-FREE ISOTOPE

The carrier-free isotope has been made available by exposure of stable sulfur to the emanations of a uranium pile. It is usually shipped as sodium acid phosphate (NaH_2PO_4) in a hypotonic solution which has a pH of approximately 2.0. Both the pH and tonicity are best adjusted prior to intravenous administration, although such is unnecessary for the oral route. Chemical neutrality, as indicated by phenol red, may be obtained by addition, dropwise, of one-tenth normal sodium hydroxide (NaOH); and tonicity may be altered toward physiological by addition of normal saline. Occasionally, distilled water will contain sufficient calcium and magnesium, as impurities, to cause precipitation of the phosphorous. According to the National Bureau of Standards, this may be obviated by the use of 0.001 molar phosphoric acid (H_3PO_4) as the dilutent. The high specific activites now available make dilution desirable. A relative concentration of 1-2 millicuries per milliliter has proved to be optimum for most therapeutic occasions.

SUBCUTANEOUS ADMINISTRATION

Subcutaneous or intramuscular administration in general is contra-indicated because of the large amount of radiation received locally during the absorptive process. Either oral or intravenous routes may be used. In the former case, sterilization is unnecessary; but, on the other hand, relatively greater dosages are required because of uncertain absorption. Absorption may be aided by giving the solution when the stomach is empty, and by withholding food for at least two hours. For the following day iron and calcium containing substances should be avoided. Within six days after oral administration to normal human subjects, 25 to 50 per cent is excreted in the urine and feces. In patients who have leukemia or polycythemia vera, excretion is somewhat less (circa 20-25 per cent of the total dose). It is common practice to consider the effective dose as being 75 per cent of the total oral one. Intravenously, absorption is, of course, 100 per cent; but excretion in six days may range from 5 per cent to 25 per cent in patients suffering from the previously indicated diseases. Nearly all such excretion is by the kidneys.

RADIOPHOSPHOROUS

Radiophosphorous is a monochromatic beta particle emitter, with a half-life of 14.3 days. The particles have a maximum energy of 1.69 M.E.V.; and they are calculated to have an approximate range of 7 mm. in human tissue. The effective dosage is highly individualized. No scheme, based on a specified amount per unit of body weight, is feasible. In general, frequent small doses seem most efficacious in the treatment of lymphoma and chronic leukemia. This is the so-called "fractional method" of Low-Beer, Lawrence, and Stone[3]. One to 2.5 millicuries per week are given, usually intravenously; and, either the amount is decreased, or the interval lengthened as the blood returns to normal. In contrast, polycythemia vera is treated with a large initial dose of 6-8 m.c. intravenously (8-10 m.c. orally). Experience has shown that remissions are longer and more consistent by this method. If one does not occur within three months, the original dose or fraction thereof may be repeated.

* Damon Runyon Sr. Clinical Research Fellow of The American Cancer Society, Inc.

** From the Department of Medicine, University of Chicago Clinics.

*** Presented by Dr. L. O. Jacobson at the International Post-Graduate Medical Assembly of Southwestern Texas and read between the dates of January 25-27, 1949.

Individual variation is marked; hence, some trial and error is unavoidable.

ALLOW FOR DECAY

In other than freshly standardized solutions, calculations of dosage must allow for decay of the radioactivity. Since radioactive decay is characteristically logarithmic, this is best done by plotting a decay curve on semi-logarithmic paper so that the mid-point corresponds to 50 per cent decay in 14.3 days. For some purposes even the hour of the day must be considered, but this is unnecessary in therapeutic use.

Radiation dosage afforded by P^{32} can be calculated in equivalent roentgens according to the formula of Marinelli[4]. Roughly, however, 0.1 millicurie per kilogram body weight, if all retained, delivers about 3 equivalent roentgens of total body radiation in the first day. The same dose would yield between 30 and 60 equivalent roentgens total radiation if less than 50 per cent were excreted. Because of the affinity for reticulo-endothelial tissues, the majority of radiation is expended there.

P^{32} FIRST USED

P^{32} was first used in the treatment of polycythemia vera by J. H. Lawrence in 1940. Since then, polycythemia has become the prime indication for its use. Numerous investigators[5-7] have measured and tabulated accurately the percentage of remissions obtained, and the duration of each. Generally, improvement in the red blood count can be expected in two weeks to three months after the initial dose; and adequate control may persist from six to forty-four months. Because of lag in response it is thought wise to reduce the hematocrit to near-normal levels (i.e. below 55 per cent) by repeated phlebotomies prior to P^{32} therapy. Thromboses are thus avoided, and the symptoms are alleviated. Commonly, about 10 per cent of all cases of polycythemia vera terminate in chronic myelogenous leukemia. An increased incidence has been said to follow P^{32} therapy; but such has not been entirely confirmed by experience. The periods of observation have not been sufficiently long to allow statistical accuracy. Until a definite answer is at hand, the advantages of P^{32} therapy in this disease hardly warrant extreme conservatism.

REINHARD REPORTS

The response of chronic myelogenous leukemia to P^{32} administration is somewhat less than the response after X-radiation. Reinhard et al[5] reported the results in 39 patients to whom they gave frequent small doses. Nearly all had symptomatic, as well as hematologic, improvement; but splenomegaly disappeared in only ten. It was felt that life was not greatly prolonged. Lawrence, Lowry, et al[8] have recently reviewed the results in 129 patients, and concluded that although the length of life was not significantly prolonged, morbidity was reduced. In general, P^{32} has no advantage over X-ray in the treatment of this disorder.

Dosage requirement in chronic lymphatic leukemia and lymphosarcoma is thought to be somewhat lower than in the previously mentioned diseases. Both usually respond satisfactorily to P^{32} in that diminution in size of affected nodes follows selective uptake by them. The spleen, too, may recede. Treatment is most effective in repeated small doses, according to the plan mentioned; but particular care is necessary in order to avoid severe leukopenia. X-radiation probably remains the treatment of choice; but P^{32} may be substituted with some success.

EQUIVOCAL RESULTS

Hodgkin's disease, multiple myeloma, malignant melanoma, Ewing's sarcoma, and mycosis fungoides have all been subjected to P^{32} therapy with notable lack of benefit. All forms of acute leukemia are essentially unaffected. Reticulum cell sarcoma and giant follicular lymphoma yield equivocal and inconsistent results.

There is no method by which an exactly appropriate dose of P^{32} can be predetermined. For this reason signs of toxicity are frequently seen. Once given, the element cannot be removed, nor can excretion be hastened. Leukopenia, thrombocytopenia, and anemia may occur in that order. Anemia is rarest of the three. Bone marrow aplasia may follow large doses; but, provided the patient can be successfully supported, it is seldom irreversible. Attention is directed to the fact that toxic signs may appear as long as four months after treatment, rather than several days as with X-radiation. The major advantages of P^{32} are lack of dose limitation by skin tolerance, absence of radiation sickness, and concentration of irradiation in diseased cells.

RADIOARSENIC (As^{76})

For nearly one hundred years arsenic has been employed empirically in the treatment of leukemia. Enthusiasm lagged until re-investigation of its potentialities by Forkner and Scott[9] in 1931. In 1947 the idea occurred to one of the authors (LOJ) that radioactive arsenic, by combining the effect of radiation and the chemical effect of arsenic, might be more potent than either alone. As a result, 26 patients were subsequently treated; and the detailed responses have been tabulated[10].

Arsenic[76] was produced by the Szilard-Chalmers reaction, which, in brief, involved irradiation of an organic stable arsenic compound (cacodylic acid) in a uranium pile, with final recovery of the desired isotope. As^{76} has a half-life of 26.8 hours, and its emanations include positrons, beta particles, and gamma rays. The latter two are quite energetic, hence, the element must be handled carefully with special equipment. General use is made more impractical by the short half-life which necessitates adjacent sites of production and administration.

METABOLIC STUDIES

Metabolic studies[11] on various organisms, including man, have shown inconsistent species differences in excretion and tissue localization of arsenic. For therapeutic purposes it may be considered that there is no selective uptake, and that any effects are due to total body radiation. It has been estimated that one millicurie of arsenic[76] will yield approximately one equivalent roentgen total body radiation. Initially, patients were given intravenously 0.5 to 2.0 millicuries, an amount that was soon found to be inadequate. As products of greater specific activity became available, doses were increased to 65, and even to 100 millicuries. Because the stable arsenic content was only 3-10 mg per dose, chemical toxicity did not occur. Prior to administration, a saline infusion was started; the arsenic trioxide solution was then drained into the open infusion bottle by means of a heavily shielded remote control mechanism.

TWENTY-FOUR TREATED

Twenty-four of the patients treated had tumors of the hematopoietic tissues; two had polycythemia vera; and one had carcinoma of the stomach with metastases. Each diagnosis was confirmed microscopically before treatment; and repeat tissue studies were done as indicated during the patients' course. Supportive measures included blood transfusions, antibiotics, digitalis, etc, as deemed necessary in each individual case. Of four patients with Hodgkin's disease, the longest remission was two months. A similar response was seen in one of two cases of acute leuke-

mia; but this has occasionally occurred spontaneously. The total white count was reduced, yet abnormal forms persisted in the circulating blood. Terminally, leukocytosis reappeared. Prolongation of life remained equivocal. In subacute myelogenous leukemia (3 cases), chronic myelogenous leukemia (6 cases), subacute lymphatic leukemia (4 cases), and chronic lymphatic leukemia (4 cases) results were inconstant. Some patients responded well, but others did not. One case of polycythemia vera improved. However, relapse was seen in three months. The one person, who had multiple myeloma, claimed subjective benefit; but objective confirmation was lacking. Neither mycosis fungoides nor gastric carcinoma responded favorably.

Although As[76] has the capacity to produce remissions in some of the diseases mentioned, it offers no advantage to other types of therapy, yet has the disadvantage of danger and clumsiness in handling.

RADIOSODIUM (Na^{24})

Radiosodium has not been used extensively in therapy of neoplastic diseases because of its energetic radiations (beta and gamma) and because of its short half-life (14.8 hours). As with arsenic, rather complicated handling techniques are required. Tracer amounts have been utilized for metabolic studies and determination of circulation times; but the therapeutic possibilities were first suggested by Hamilton and Stone[12] in 1937. Thygesen, Videboeck, and Villaume[13] expanded the observations in 1944, and rather extensive clinical trials were recorded by Evans et al[14] in 1948. The latter investigators administered radiosodium orally as the chloride. Absorption was prompt and complete; distribution was general; and excretion was less than 10 per cent. They considered results to be satisfactory in chronic myelogenous leukemia, chronic lymphatic leukemia, and polycythemia vera. Doses varied from 2 millicuries per week to 40 millicuries per month, and depended largely on the individual response. Inasmuch as selective uptake was absent, effective action was attributed to total body radiation. It was concluded that Na^{24} yielded results comparable to, but no better than, other forms of radiation therapy.

RADIOIODINE (I^{131})

Radioiodine is not used in the general treatment of neoplastic disease. Because of its high selectivity for thyroid tissue, indications have been restricted almost entirely to diseases of that gland. In tracer doses it is rapidly becoming a valuable diagnostic tool. Selected cases of hyperthyroidism, secondary to diffuse thyroid hyperplasia, have been found to respond to larger doses. Extremely large doses are frequently palliative in thyroid carcinoma. Response is variable, and seems to depend upon the ability of the cells to metabolize iodine, which in turn, is positively correlated with their functional capacity. In a few cases the latter has been enhanced by prior administration of thyrotropic hormone. A complete resume of radioiodine chemistry, dosimetry, and biological utilization has been compiled.[15]

NITROGEN MUSTARD

For protection against the devastating action of sulfur containing mustard gas in World War I, a thorough investigation into its pharmacological properties was instituted.[16] Similarly, during World War II, after the Germans had developed nitrogen analogues of sulfur mustard (the nitrogen mustards), such investigation was extended. It was soon recognized that the more rapidly multiplying tissues, i.e. bone marrow, lymphatics, and gastro-intestinal epithelium were preferentially attacked; and from this observation arose the idea of using the agent in treatment of diseases of these tissues. Chemical variants were promptly surveyed in this respect. Results with the Tris form (betachloro-eythlamine) were reported by Gilman and Phillips[17] in 1946. Clinical use of the methyl bis form (betachloroethylamine) was begun by Jacobson et al in 1942 and reported in 1946.[18] Simultaneous data was published by Goodman, et al[19] in 1946. Subsequent comparison of results has established the moderate superiority of the Bis compound.

ACTION UNCLEAR

The mode of action of nitrogen mustards is unclear. Rhoads[20] pointed out the similarity of effects to those of radiation. Mitotic division is inhibited, nuclei are fragmented, and cells become non-viable. Proliferation is presumably influenced much more than differentiation. In vitro, growth of yeasts and cleavage of sea urchin eggs can be prevented by dilute nitrogen mustard solutions. The chemically active agent is thought to be the eythlenimonium derivative, which is formed spontaneously as the white powder is mixed with water.

Inasmuch as this occurs rapidly and is short-lived, mixing should be done immediately (not more than 5 minutes) before administration to the patient. Physiological saline is started intravenously; and the freshly prepared mustard solution is injected into the tubing. The remainder of the 500 cc of saline is then flushed through the apparatus in order to prevent thrombophlebitis, and in order to help replace chlorides lost in subsequent vomiting. Because of direct chemical action on gastric mucosa, severe nausea and vomiting may begin within two or three hours. Heavy sedation, including barbiturates and demerol, is useful in minimizing this; although the exact amount is an individual matter. Customarily sodium amytal, 3 grs (0.2 Gm) orally, precedes the process by one-half hour. Two or three hours later 50 mgs. of demerol are given intramuscularly. After that, severity of reaction is the sole guide.

By trial and error an optimum dosage of 0.1 mg, nitrogen mustard per kilogram of body weight, given on consecutive days for four doses, has been established. Recently it has been found feasible to increase the total amount by giving 0.2 mg, 0.1 mg, and 0.2 mg per kilogram body weight respectively on consecutive days; but 0.3 mg per kilogram body weight daily for two days lead to sufficiently severe toxicity as to be impractical.

NITROGEN MUSTARD

Nitrogen mustard therapy has been employed in a multitude of diseases, with variable results. Perhaps the prime indication is Hodgkin's disease, although it is recognized that X-radiation may be superior as far as length of remission is concerned. The policy of the Hematology Department of the University of Chicago is rapidly becoming one of using X-ray when the involved nodes are localized, and nitrogen mustard when they are diffuse or widely separated. In a favorable case lymphadenopathy may begin to subside 3 to 7 days after nitrogen mustard therapy, and may have disappeared entirely by the end of three weeks. Although "resistance" per se probably does not develop, succeeding courses may become progressively less effective. Length of remissions varies from one to ten months; yet one patient, who had previously received large amounts of X-ray without notable benefit, was free from abnormal signs or symptoms for twenty-

four months after the first course of nitrogen mustards. Another individual received twenty-two courses in seven years, and finally succumbed to an overwhelming tuberculous infection with meningitis. At autopsy Hodgkin's tissue was minimal in amount, and largely limited to the mediastinum. It must be emphasized, however, that the action is similar to radiation, and serves only to retard the process.

FAVORABLY AFFECTED

Chronic lymphatic leukemia, lymphosarcoma, and polycythemia vera are usually affected favorably by nitrogen mustard. Although X-ray remains the treatment of choice in the former two, remissions of 2 to 24 months and 1 to 10 months respectively have been obtained with nitrogen mustard. Polycythemia vera apparently responds as readily to it as to P^{32}. Ten cases have been treated in this clinic to date, and they are to be reported in detail. Remissions as long as three years have been observed. Though benefit in cases of the diseases just mentioned is frequent, it is by no means constant. As a rule, those which are resistant to X-ray are also resistant to nitrogen mustard; but this, too, is not thoroughly consistent.

Chronic myelogenous leukemia, all forms of acute leukemia, and multiple myeloma are either unaffected or benefited to an insignificant degree by nitrogen mustard therapy. A small percentage of patients may experience short term palliation of severe symptoms; but the inexorable progress of the disease is unaltered. Various carcinomas, and more unusual tumors, such as sympathicoblastoma or hypernephroma have been treated with similar lack of success.

INHERENT DANGERS

Administration of nitrogen mustard is attended by the same inherent dangers as X-ray therapy. Single courses may be followed by leukopenia, thrombocytopenia, and more rarely anemia. Penicillin, and other antibiotics, have dispelled most of the customary apprehension over granulocytopenia. The idea is rapidly becoming accepted that absolute polymorphonuclear values of 1000-1200 per cmm. do not contra-indicate treatment, providing the disease process requires such, and the patient can be under careful observation. Aplasia of the hematopoietic elements of the bone marrow is known to occur[21]; but seldom is this irreversible. In 700 cases only two were the cause of any concern on this point. Recovery is usually orderly and complete. The degenerating phase may begin within twenty-four hours after completion of the course. By fourteen days the atrophic phase is usually finished, and by thirty days complete regeneration, with mild compensatory hyperplasia, has occurred. A less appreciated delayed effect of nitrogen mustard toxicity is defective blood coagulation[22], over and above that which might result from thrombocytopenia. Clotting time is prolonged, and presence of a circulating heparinoid substance can be detected by the heparin tolerance test. Intravenous toluidine blue (2 mg per kg. body weight) diluted in saline, or protamine sulfate (50 mg) intramuscularly have been found to be effective treatment. Reactivation of previously healed tuberculous foci is a possibility which must always be carefully considered. In the last twelve months two patients have died in this hospital of widespread miliary tuberculosis, presumably precipitated by nitrogen mustard treatment. Repeated precautionary examinations must be done in anticipation of this. Of the immediate toxic effects, nausea, vomiting, diarrhea, and thrombophlebitis are the only important ones. Only the latter is not self-limited.

URETHANE

Urethane (ethyl carbamate) action in depressing the number of circulating lymphocytes was investigated as early as 1925[23]. Haddow, Paterson, et al[24] were first to observe its effect in human leukemia. Since that time, several series of similarly treated patients have been recorded[25-27]. The mode of action of this drug is obscure. Phenyl carbamate was found to arrest mitotic division in a manner similar to colchicine. Eythl carbamate was even more efficacious. Some evidence exists that its action may be mediated through inhibition of the cytochrome oxidation-reduction system; yet other investigators suggest that nucleotide biosynthesis is retarded by interference with purine metabolism.

English therapists have administered urethane mostly in the form of solutions, flavored with appropriate syrups. In America enteric coated tablets are favored for moderate doses, and intramuscular injection of a 40-50 per cent solution for large amounts. Whatever the route, nausea is a common sequella, even though an average dose is only 3-4 gms per day.

COMPARABLE TO X-RAY

Urethane is most effective in chronic myelogenous leukemia. Granulocytes may be almost specifically inhibited, and the bone marrow may resemble that seen in agranulocytosis. Haddow, Paterson, et al[24] found its action comparable to that of X-ray. Of thirteen cases reported, all experienced reduction of circulating leukocytes to 20,000 per cmm or less within thirty-six days; and less mature elements were affected first. Total doses varied from 19 to 134 grams. Cases in which both urethane and X-ray were used gave no evidence either of potentiation or of mutual inhibition.

Response of chronic lymphatic leukemia to urethane is variable. Remissions, if produced, seem to be shorter than with other modes of treatment. There is no prophylactic effect if given during a remission. Trial has been extended to many neoplastic diseases, including multiple myeloma, Hodgkin's disease, lymphosarcoma, seminoma, and various carcinomas without benefit. Occasionally there is subjective palliation; but this is inconstant.

Toxic effects are similar to those following nitrogen mustard therapy, and consist chiefly of bone marrow depression and vomiting.

FOLIC ACID ANTAGONISTS

The demonstration that breast cancer in mice could be significantly inhibited by folic acid lead to its subsequent trial in humans. In the initial group of patients were eleven children with acute leukemia. The reticulo-endothelial systems in these individuals were observed to be stimulated rather than inhibited; thus the idea of folic acid "antagonists" presented itself. These were synthesized and then tested in vitro by biological titration against folic acid with growth rate of Streptococcus fecalis or Lactobacillus casei as an indicator. The first compounds were quite toxic, but effective enough to be encouraging. Finally aminopterin (4-aminopteroyl glutamic acid) was tried; and impressive remissions were first observed in November, 1947. Subsequent results have recently been reported[28].

NO FIXED DOSAGE

Heretofore, all therapeutic agents have been without benefit in acute leukemia. This does not apply to folic acid antagonists. On the contrary, they are relatively ineffective in the chronic leukemia. Aminopterin is given intramuscularly in daily amounts of 0.5 to 1.0 mg for children, and 1-4 mgs for adults. Because of frequent and severe toxicity, these amounts are given until a remission occurs, and then reduced to a more easily tolerated maintenance dose. Variable individual responses preclude a fixed dosage schedule. Overdosage may result in bone marrow aplasia,

stomatitis, melena, gastro-intestinal ulcerations, or megaloblastic anemia. Large amounts of folic acid do not alleviate these symptoms, unless the medication is discontinued. A general hemorrhagic tendency, similar to that seen after radiation [29] may occur, but can usually be adequately controlled with protamine sulfate or toluidine blue.

When aminopterin is effective in acute leukemia, immature white cells disappear from the circulation, red cells and platelets shift in a favorable direction, and the bone marrow reverts toward normal. Clinical improvement may be marked; but remissions are short-lived. Because of variations in the natural course of leukemia it is difficult to prove that significant alterations have been produced by folic acid antagonists; yet it is important that a synthetic compound has been found which will cause the bone marrow to change so that, temporarily, it cannot be distinguished from normal. It is hoped that more efficacious and less toxic substances will be discovered in the near future.

MISCELLANEOUS

In addition to the preceding established therapeutic agents, others have been tried, found to have some beneficial effect, and then discarded for one reason or another. The fact that they have not withstood the test of clinical application is overshadowed by the fact that they represent proof of carcinocidal effect of diverse synthetic compounds. Successful chemical treatment of neoplastic disease may well be brought closer by such observations.

Clinical alleviation, by administration of stillbamidine (diamidino-stilbene-di-isothionate) of patients suffering from multiple myeloma was first reported by Snapper[30] in 1946. Of ten patients, 9 were observed to be improved. Specific morphological changes in myeloma cells were recognized[31]; and interference with protamine ribonucleate metabolism was postulated. Subsequent trial by many therapists have shown that clinical improvement is not so constant as originally thought; hence, clinical use is decreasing.

Bacterial polysaccharide from Serratia marcesens, as well as from other organisms (e.g. Coley's mixed polysaccharides) have been found to have a destructive effect on many animal tumors. The necessary dose for human beings is extremely pyrogenic. Because of this, and because of unpredictable response, clinical use has been largely discontinued.

PROFOUND EFFECT

In studies on the action of colchicine in the deranged purine metabolism of gout, the presence of a

TABLE I

		P^{32}	As^{76}	Na^{24}	I^{131}	Nitrogen Mustard	Urethane	Folic Acid Antagonists	X-ray
Myelogenous Leukemia	Acute	O	±	±	—	O	O	++	O
	Chronic	+	++	++	—	±	+++	O	+++
Lymphatic Leukemia	Acute	O	±	O	—	O	O	++	O
	Chronic	++	+	++	—	++	++	O	+++
Lymphosarcoma		++	—	+	—	++	+	—	+++
Hodgkin's Disease		O	O	+	—	+++	O	—	+++
Giant Follicular Lymphoma		±	—	—	—	+++	±	—	+++
Polycythemia Vera		+++	++	+++	—	+++	O	—	++
Multiple Myeloma		O	+	—	—	O	O	—	±
Reticulum Cell Sarcoma		±	—	—	—	+	O	—	++
Mycosis Fungoides		O	O	—	—	+	O	—	++
Carcinoma		±	O	—	Thyroid	O	O	—	±

— Not tried
O No effect
± Inconstant effect
+ Subjectively beneficial
++ Objective evidence of benefit
+++ Usually followed by remission

profound effect on nuclear metabolism became evident. Soon thereafter significant regression of animal tumors was demonstrated. In human beings, however, the difference between effective and toxic doses was too small to be practical.

Compound E of Kendall, adrenocorticotropic hormone (ACTH), and adrenocortical hormones are known to cause a decrease in the number of circulating lymphocytes, as well as general depression of lymphoid tissue. At autopsy, many of the hematological diseases are accompanied by gross hypertrophy of the adrenal cortices. Administration of the above compounds has been shown to have a slight inhibitory action in animal lymphomas. Experience in the human being is as yet incomplete.

The most recent metabolic inhibitor, Quanozolo, is known to depress growth of certain animal cancers[32], presumably by selective competition with guanine in purine metabolism. Inhibition, rather than destruction, of cells is postulated. Reports of clinical use are awaited.

SUMMARY

A summary of the therapeutic effectiveness of certain of the radioactive elements and chemotherapeutic agents is given in Table I.

CONCLUSIONS

1. The more recent radioactive and chemical agents employed in the treatment of neoplastic diseases are reviewed; and relative results are given.
2. Despite recent advances, X-ray probably remains the treatment of choice in all such diseases, with exception of acute leukemia.

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BOOK REVIEW

NAVAJOS, GODS, AND TOM-TOMS: S. H. Babington, M. D., F. I. C. S., Greenberg: Publisher, 1950. Price - $3.50 - pp 242.

Dr. Babington has written a narrative account of his experiences with the Navajos. The doctor is a practicing surgeon, and his observation of the Navajo tribe and their customs is that of a physician. He has been particularly interested in the various healing ceremonies, and in the various methods of treatment used by the native healers. His observations are timely. In these days when we are beginning to treat the patient as a human being, not an organism, we find ourselves depending on psychosomatic medicine more and more.

As one reads this account, one is struck by the fact that apparently the native medicine men are able to apply psychosomatic therapy perhaps a great deal better than many of us who are in the active practice of medicine. It should be of great interest to physicians in the Southwest to know how much the Indian medicine man depends on the native herbs. The most common herbs, grasses, etc. are all put to use. For example, the Jimson weed serves as a definite narcotic. Greasewood and sagebrush are considered to be wonderful aids to a delivery, and surprisingly enough, the lowly buttercup in powder form is taken every morning for syphilis.

Dr. Babington has lived among these people. He has studied their customs, and he has written an extremely interesting treatise that should be read by all the readers of SOUTHWESTERN MEDICINE. The Navajos are our neighbors, and I believe that the reading of this interesting volume will lead us to understand their customs and viewpoints more fully, to the advantage of all concerned. — L. C. F.

THE CERVICAL SYNDROME

By Ruth Jackson, M. D., Dallas, Texas

Cervical Syndrome is a term used to classify a group of cases which present definitely similar symptoms and clinical findings, the causative factor of which is irritation of the cervical nerve roots. To adequately interpret this syndrome one must have a knowledge of the anatomy and mechanics of the cervical spine, the segmental character of the cervical nerves, and the relationship between the cervical nerves and the sympathetic nervous system.

The facets of the cervical vertebrae are designed so that a great range of motion in all directions is possible. The foramina through which the nerve roots pass are bony canals, the posterior walls of which are formed by the articular processes of the adjacent vertebrae, and the anterior walls and floors of which are formed by the grooves in the roots of the vertebral arches. The nerve roots leave the spinal cord at an angle which approximates a right angle, and they fill fairly snugly the foramina through which they pass. This makes them very vulnerable to irritation from any mechanical derangement of the cervical spine. Irritation of these nerve roots occurs before they divide into anterior and posterior primary rami.

DISTRIBUTION SEGMENTAL

The distribution of the nerve roots is segmental in character. There is a definite overlap of the nerve supply to adjacent segments in any given skin area. Painful irritations or stimulation of a muscle may cause pain anywhere along the segmental distribution of the nerve. For instance, irritation of the dome of the diaphragm or the pericardium may cause pain in any of the muscles or areas supplied by the fourth cervical nerve root and vice-versa. The segmental distribution of the cervical nerve roots, the sensory overlap, and the reflex phenomenon of pain make the exact localization of nerve root irritation somewhat difficult.

The cervical nerve roots are composed of motor and sensory fibers only as compared with the thoracic and upper two lumbar nerve roots which contain sympathetic fibers, or white rami communicantes. The sympathetic nervous system has its connection with the cervical nerve roots through the upper two thoracic nerves which join the cervical part of the sympathetic trunk via their anterior primary rami, and proceed upwards to the cervical ganglia. From the superior cervical sympathetic ganglia gray rami communicantes pass to the undivided primary rami of the upper four cervical nerves. Two gray rami-communicantes from the middle cervical ganglia and two from the inferior cervical ganglia pass to the undivided primary rami of the lower four cervical nerves. Other gray rami communicantes, or post ganglionic fibers, pass along the internal carotid and opthalmic arteries to reach the orbit where they supply the back of the orbit, the vessels of the eyeball, the dilator muscle of the pupil and the smooth muscle of the upper eyelid. Irritation of these post ganglionic fibers may produce symptoms and clinical findings, such as: blurring of vision and vertigo, dilatation of the pupil, and ptosis of the upper eyelid on the side of the irritation, which may appear to have no relationship to the other symptoms and clinical findings associated with irritation of the cervical nerve roots.

IRRITATION OF ROOTS

Irritation of the cervical nerve roots occurs as a result of some mechanical derangement in or about the intervertebral foramina. The most common cause of irritation is abnormal motions, or subluxations of the joints of the cervical spine which occur because of sprain, stretching, or relaxation of the ligamentous and capsular structures. Ruptured or protruding intervertebral discs, hypertrophic changes and osteophyte formation in or about the intervertebral foramina, swelling of the capsular structures from inflammatory and allergic reactions or from hemorrhage may cause irritation of the nerve roots. Any sudden unguarded motion of the neck or any prolonged relaxation of the neck in an abnormal position may cause a subluxation with actual locking of the facets on one side. Other causative factors may be due to relaxation of the supporting structures of the cervical spine which may be part of a general process due to illness or increasing age, or to generally poor posture. The thoughtless roughness in the handling of patients when under a general anesthetic has been responsible for cervical nerve root irritation in many instances.

The amount of irritation and hence the symptoms and clinical findings are not dependent upon the extent of the derangement, in-as-much-as minimal derangements may produce severe symptoms and marked derangements may cause only mild symptoms. Individual variations in the mechanics involved and in the pain threshold may account for this.

WHIP-LASH INJURIES

The whip-lash type of injury, as described by Davis, is responsible for the greatest percentage of cervical nerve root irritations. Any injury which causes a sudden forceful movement of the neck, depending on the direction of the force, with a sudden recoil in the opposite direction may be called a whip-lash. Such injuries cause typical sprains of varying degrees with subluxation of the articular processes and stretching, tearing, or avulsion of the ligamentous and capsular structures. Automobile accidents are responsible for the greatest number of such injuries. However, falls, blows on the head or chin, a sudden forceful pull on the arms, and many other apparently trivial injuries may cause a whip-lash, or a sudden "popping" of the neck. Symptoms may occur immediately or may be delayed weeks, months, or years. Usually the injury is considered insignificant, but as time passes there occurs further stretching of the ligamentous and capsular structures which allows more abnormal motions or subluxations of the joints with resulting nerve root irritations.

Rupture or protrusion of one or more intervertebral discs may occur at the time of the injury, or much later as the result of some very trivial injury, in-as-much-as the relaxation of the ligamentous and capsular support makes the discs more vulnerable to rupture. Ruptured discs may or may not cause immediate nerve root irritation. This is dependent upon the location of the protrusion or herniation.

POOR POSTURE

Not infrequently cervical nerve root irritation is caused by poor general posture. Markedly rounded shoulders cause an increase in hyperextension of the neck which may eventually cause subluxations to occur. The loose-jointed type of posture predisposes to nerve root irritation.

Cervical nerve root irritation may occur at any age, but the greatest number of patients who seek relief of their symptoms are in the third and fourth decades of life.

The diagnosis of nerve root irritation is based on the history, symptoms, clinical and X-ray findings. It

must be remembered, however, that the exact localization of the irritated nerve root is difficult because of the segmental character of the distribution of the cervical nerves and because of the overlap of the cutaneous nerve supply, and because of the lack of clinical criteria for differentiation. However, the symptoms and clinical findings are not dependent upon the cause of the irritation.

A careful history will reveal an injury to the neck which may have occurred immediately preceeding the onset of the symptoms or weeks, months, or years before. Usually the injury itself is of little significance to the patient.

400 CASES

An analysis of the histories on 400 cases with cervical nerve root irritation has revealed that all cases can be grouped according to their symptoms. Every case will fall into one of the following classifications.

1. Patients with acute symptoms following a recent injury.
2. Patients with chronic symptoms of long duration.
3. Patients with severely acute well localized pain who have had previous chronic symptoms.

The acute symptoms in this third group of cases are always caused by sudden motion of the neck, such as: stooping over suddenly to brush the teeth, wash the face, or to pick up something which causes a sudden hyperextension of the neck; throwing a ball or any other object which causes a sudden turning of the head; reaching over the back of an automobile seat, or any other seat; catching oneself with the hand or shoulder to prevent a fall, turning over in bed, and many other apparently simple activities. This group of patients usually get sudden severe pain in the tip of the shoulder, which makes them think the shoulder has been injured, or they get severe pain in the chest, or in the muscles of the posterior part of the shoulder girdle so that they think they have pleurisy.

STIFFNESS AND PAIN

Regardless of which nerve root or roots may be irritated all patients have a certain amount of stiffness and pain in the neck, and many give a history of "cricks" in the neck. If the upper roots, C2, C3 and C4 are irritated, they may complain of occipital headaches which are often typical of migraine, blurring of vision, dizziness and nausea especially when attempting to lie down, numbness of the side of the neck, tension and "knots" in the neck muscles and swelling and stiffness of the fingers. If the 4th and perhaps the 5th nerve roots are irritated they may complain of shortness of breath, palpitation of the heart, pain in the chest, and localized pain in the muscles between the neck and the shoulder joint or between or about the shoulder blades. The pain may occur on either or both sides of the body or on first one side and then the other.

Involvement of the fifth nerve root which, according to our analysis, is the most frequent and may cause pain between the shoulders, pain in the chest, pain at the tip of the shoulder and/or in the middle of the arm and sometimes just below the elbow on the top of the forearm, and numbness and tingling of the thumb and/or index finger. Stiffness of the shoulder and/or weakness of the arm with inability to comb the hair, fasten a brassiere, or to reach the hip pocket are frequent complaints. Irritation of the sixth and seventh nerve roots may cause pain in the shoulder, arm, forearm, chest and numbness and tingling of the index, middle and perhaps the ring fingers.

VARIED SYMPTOMS

All or any of the symptoms may be acute or chronic or intermittent. Usually the symptoms are multiple and if they are chronic the patients have been treated for neuritis, migraine, arthritis, bursitis, fibrositis or fascitis.

In all instances the symptoms are aggravated by certain motions and positions of the neck. Sewing, reading, driving a car, or any occupation or pleasure which necessitates holding the neck in flexion, hyperextension, rotation or lateral bending for any length of time increase the symptoms. Aggravation of symptoms are found in women just prior to, or during, menstruation and in both sexes during upper respiratory infections, and by emotional strain and fatigue. In most instances the symptoms are worse at night and the patients have difficulty sleeping. Many patients sleep on more than one pillow, in an effort to get away from the pain which causes flexion of the neck. Some sleep without any pillow which leaves no support beneath the neck, and some sleep in the prone position which necessitates marked rotation of the neck. All these positions, as well as the relaxation of the supporting structures of the neck during sleep tend to aggravate the symptoms.

CLINICAL FINDINGS

The clinical findings vary somewhat with the nerve roots involved, but all have certain findings in common. Localized tender areas are found anywhere along the segmental distribution of the nerve roots. All patients have variable amounts of limitation of motion of the neck in lateral bending, rotation, flexion and extension, and tenderness just lateral to the spinous processes of the neck on one or both sides. Localized myalgic areas and muscle spasm in the ridge and lower portion of the trapezius and in the supraspinatus muscle or tendon are fairly constant findings in fourth nerve root irritation. In fifth nerve root irritation such areas are found in the rhomboid muscles, at the tip of the shoulder, at the insertion of the deltoid, and not infrequently in the extensor muscles of the forearm.

Tenderness in the anterior and lateral chest wall is often found. Varying degrees of limitation of glenohumeral motion in abduction, internal and external rotation occurs in about twenty (20) percent of these cases. This is due to pain and to an adhesive capsulitis, which results from the prolonged protective reaction of voluntary immobilization. Many of these patients develop calcareous deposits in the tendons, (usually the supraspinatus) of the musculotendinous cuff. The deposition of calcium in this region is doubtless due to the circulatory changes which occur as a result of muscle spasm and limitation of motion. Paresthesia over the distribution of the cutaneous branch of the axillary nerve occurs almost constantly. The biceps and triceps reflexes may be altered or absent in 5th, 6th, and 7th nerve root irritation; and there may be in a small percentage of cases paraesthesias of the thumb and fingers.

Pressure over the involved nerve root or roots and the compression test may reproduce the radicular pain, but do not give much added information as far as diagnosis is concerned. Whatever the causative mechanism of nerve root irritation the clinical findings are the same. Perhaps electromyography may be of some value in localization and differentiation of the irritative factors.

Again, we repeat, the segmental character of the cervical nerves and the sensory over-lap make exact localization of the nerve root or roots involved difficult. We believe that irritation of a single nerve root occurs in only a small percentage of cases, which accounts for the multiplicity of symptoms and clinical findings. However, many of the findings are difficult to understand on the basis of an exact anatomical explanation. For example, why should an injection of novocaine about the fourth nerve root cause momentary pain, or tingling of the little and ring fingers?

X-RAY FINDINGS

X-ray films of the cervical spine should be made in all cases. We use the technique described by Davis. Three lateral views are made with the patient in the upright position and with the X-ray tube at seventy-two (72) inches from the casette. The films are made with the patient looking straight ahead, with the chin on the chest, and in hyperextension. The straight lateral position reveals the presence of muscle spasm of the neck muscles as evidenced by the obliteration of the normal forward curve of the cervical spine and in some cases a segmental reversal of the curve. The chin-on-the-chest position reveals forward subluxations and the hyperextension position reveals posterior subluxations of the bodies of the vertebrae. It must be remembered, however, that the amount or extent of the subluxations is not indicative of the amount or extent of the nerve root irritation. Marked mechanical derangements may produce minimal symptoms, and slight mechanical derangements may produce severe symptoms! We believe that subluxations in the cervical spine are abnormal and occur because of stretching, tearing or undue relaxation of the ligamentous and capsular structures, although some radiologists disagree with this opinion.

SINGLE SUBLUXATIONS

Single subluxations occur in about fifteen per cent of the cases, and about one half of these occur between C4 and C5. Approximately one per cent occur between C3 and C4, one per cent between C5 and C6, and five tenths (0.5%) between C2 and C3 and eighty to eighty-five per cent of the cases show more than one subluxation and some of these show as many as four subluxations. The greatest percentage of two or more subluxations occur above the 5th cervical vertebrae.

Approximately forty per cent of our cases have shown definite narrowing of one or more intervertebral spaces. This is indicative of ruptured discs, but there is no way of ascertaining from the X-ray films just when the rupture occurred. Hypertrophic changes, marginal lipping or osteophyte formation do not indicate how long a ruptured disc has been present, nor do they indicate the age of the patient. These changes are initiated by the mechanical derangement; and for psychological reasons they should not be designated as arthritis. Nature is only making an effort to overcome the mechanical stress and strain by attempting to immobilize the adjacent vertebrae. We have noted that fixation of the vertebrae adjacent to a narrowed disc is a constant finding and that motion and subluxations occur above or below these vertebrae. The onset of acute episodes in most of these cases is due to a recent sprain or injury with nerve root irritation above or below the level of the fixed vertebrae.

OBLIQUE POSITION

X-ray films made in the oblique position may give additional information concerning the foramina. Hypertrophic changes or spur formation projecting into the intervertebral foramina, and anterio-posterior narrowing of the foramina can be demonstrated in the oblique views.

In 90% of our patients who have given occipital headaches or migraine as a symptom we have found subluxations of C2 on C3, and of C3 on C4, in the other 10%. This leads us to believe that irritation of the third nerve root is responsible for most of the headaches. However, there may be a sympathetic factor responsible for these headaches due to irritation of the post ganglionic fibers from the superior cervical ganglion. This accounts for the blurring of vision and the dilation of the pupil on the side of the nerve root irritation. (Opposite Horner's syndrome).

TREATMENT

The severity and duration of the symptoms, the clinical and X-ray findings govern the treatment of these cases; and in any event the treatment must be individualized. Conservative or non-surgical treatment will give the best results. From the beginning the patient should be taught that the symptoms can be relieved by fairly simple measures, but that he must adjust his activities to the mechanical derangement of his neck.

Patients who are seen immediately following an injury to the neck should have the benefit of some type of collar immobilization for about three weeks. If there is actual locking of the facets, two per cent novocaine should be injected about the involved facets. It may be necessary to apply halter traction for two to four days before the collar is applied. The correct application of the traction is extremely important. The knees should be flexed and the head elevated to prevent the pull on, and the pain in, the abdominal muscles. The line of traction should be straight and either flexion or hyperextension should be avoided.

NOVOCAINE INJECTION

The patients with sub-acute and chronic symptoms may require the injection of novocaine into the myalgic areas for relief of pain. The injection may be made in the neck muscles and about the involved nerve root or roots. Breaking the pain reflex with a local anaesthetic, if done correctly, gives immediate relief of pain which lasts for days, weeks, or months. There may be some residual soreness from the injection for two or three days, but the acute symptoms will subside at once. Diathermy treatments daily or three times each week help to relieve pain and muscle spasm.

If the general posture is poor, shoulder straps are often of great value in the relief of pain and discomfort. Correct postural habits must be taught, and the patients should know the mechanics involved for the relief of symptoms and the prevention of future attacks. They should avoid holding the neck in flexion or hyperextension for any length of time. Reading stands to hold the reading material at eye level, lowering desk chairs or raising desks, raising the auto seat, and many other simple adjustments are of great benefit.

Because many patients complained of aggravation of symptoms while in bed, and because correct sleeping posture is important in the treatment of these patients, we designed a special pillow, which has been our greatest adjunct in treatment. The pillow fits the normal contour of the neck and keeps the neck straight while the patient is sleeping. The conventional pillow causes flexion of the neck and aggravates the symptoms. In some instances the "contour pillow" without other treatment, gives relief of symptoms.

STIFF SHOULDERS

The stiff shoulders should be treated by novocaine injections, diathermy, and intensive physical therapy. Vitamin E given intra-muscularly and tolserol by mouth in the sub-acute and chronic cases give relief of muscle spasm or tension in many instances. Emotional stress and strain should be eliminated in all cases, if possible.

The importance of cervical investigation in any patient with shoulder and arm pain and/or disability in the absence of actual trauma to the shoulder or arm cannot be over stressed. The usual diagnosis of neuritis, bursitis, periarthritis, myositis, fibrositis, and myofascitis of the shoulder and arm should not be made until cervical nerve root irritation has been ruled out entirely. Usually these conditions are only manifestations of cervical nerve root irritation.

HAVERHILL FEVER (ERYTHEMA ARTHRITICUM EPIDEMICUM) DISCUSSION OF THE JOINT MANIFESTATIONS*

By Robert A. Morse, M. D., Hermann Hospital and Baylor University College of Medicine, Houston

Haverhill Fever (Erythema Arthriticum Epidemicum) is a disease which is rarely considered in the differential diagnosis of acute infectious arthritis because it is a rare disease which comparatively few of us have had the opportunity to observe and study. The disease is defined as an acute infectious disease manifested by an abrupt onset with chills, fever, and malaise; an early skin eruption, and multiple arthritis; having a relapsing course of four to eight weeks duration with spontaneous recovery.[1] It was first described in 1926 by Place, Sutton, and Willner[2] who reported an epidemic of eighty-six cases which occurred in the city of Haverhill, Massachusetts. Since that time forty-six sporadic cases have been reported, primarily from the New England and Middle Atlantic states, with a few from the Middle Western and Southeastern states. One case was reported from Dallas in 1946,[3] and we observed one case in Houston in 1948.[4]

ETIOLOGIC AGENT

The etiologic agent is the Haverhillia multiformis (streptobacillus moniliformis), a small, extremely pleomorphic, gram-negative rod which is grown with some difficulty.[5] The organism is a normal inhabitant of the naso-pharynx of the rat, and usual mode of transmission is via the bite of a rat. In the original Haverhill epidemic the milk supply was suspected to be the source of the infection. There have been approximately sixteen cases reported in the literature in which no rat bite was present and the portal of entry was not known. The association of this disease with the bite of a rat has led to considerable confusion with the more common form of Rat-Bite Fever (Soduku) which is due to infection by the Spirillum minus. A clinical differentiation is possible by the fact that Soduku is not characteristically associated with rheumatic manifestations.

ARTHRITIS OBSERVED

Arthritis of some degree has been observed in approximately seventy per cent of the reported cases.[6] In the original report of the disease the arthritis was the most persistant symptom. It became apparent between the first and the fourth day of the disease and was almost always multiple, usually involving the large joints. The joints varied from subjective pain with no objective findings to well marked swelling and redness with effusion into the joint. The joint manifestations subsided soon after the subsidence of the fever usually leaving no residua. The wrists and elbows have been the joints most commonly involved, then the knees, shoulders, fingers, and ankles. Tenderness, pain on motion, increased local heat, periarticular swelling and edema, and varying degrees of intra-articular effusion are usually present. In most of the reported cases roentgenographic examination of the involved joints has shown only widening of the joint spaces and periarticular thickening. However, evidence of bone destruction has been reported.[1,7] In general the involved joints have completely subsided, leaving no residua. A few cases have been reported in which follow-up for a two year period or longer has revealed persistent, recurrent swelling and pain.[1,7] No permanent crippling of joint function has been noted.

FATAL CASE

Our case, a fatal one, was followed for a period of eighteen months. During that time the patient had three acute episodes of fever and multiple arthritis of eight, fourteen, and eight weeks duration, and the terminal recurrance which lasted seventeen days. The recurrances were separated by complete remissions lasting four, three, and thirty-six weeks. During the exacerbations the patient had severe arthritis involving the fingers, wrists, elbows, knees, and ankles. The joints were swollen, hot, tender, and painful on motion, and there was marked periarticular swelling and effusion into all of the involved joints. With the remissions in the disease the joint manifestations subsided and the joints became objectively and subjectively normal.

The fluid aspirated on several occasions from the knee joints of this patient was viscid, somewhat cloudy, and congealed almost immediately. Microscopic examination revealed the cellular elements to be ninety per cent polymorphonuclear neutrophiles. The Haverhillia multiformis was cultured from the fluid on several occasions.

DIAGNOSIS

The diagnosis can be suspected by the clinical picture of an abrupt onset with chills and fever; an early, generalized, maculo-papular skin eruption; and multiple arthritis. The suspicion is strengthened if a history of previous rat bite is obtained. The confirmation of the diagnosis is the demonstration of the Haverhillia multiformis by culture of the blood or joint aspirate, or both, on protein-enriched media under anaerobic conditions.

Prior to the introduction of penicillin, treatment was non-specific and supportive. Autogenous vaccines,[8] arsenicals,[7] and sulfonamides[9] were of no value. Penicillin has been proven to be successful in the treatment of a number of cases.[10,11] One reported case which did not respond to penicillin was successfully treated with streptomycin.[12] Our case failed to respond to either antibiotic, and in vitro the organisms were inhibited only in very high concentrations of the drug.

SUMMARY

1. A brief review of the arthritic manifestations of Haverhill Fever (Erythema Arthriticum Epitemicum) is presented.

2. It is pointed out that two cases have appeared in this section of the country within the last four years.

3. It is suggested that this disease should be considered in the differential diagnosis of unexplained acute and/or chronic arthritis associated with fever, especially if there is a history of previous rat bite.

4. The diagnosis is confirmed by culture of the

* Delivered before the Texas Rheumatism Association in San Antonio, 1949.

etiologic agent, Haverhillia multiformis, from the blood and/or joint aspirate.

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Prophylactic Treatment of Rheumatic Fever

The studies at the House of the Good Samaritan (Boston) have been summarized as follows by Sturgis[1]. "Massell, Dow, and Jones[2] reported in 1948 that 15 patients with rheumatic fever who were promptly treated with penicillin for clinical or subclinical hemolytic streptococcal infections did not get recurrences of rheumatic fever. For the past two years, Sturgis, Massell, and others have been collecting further data. This has been done not only on hospitalized patients, but also on a group of rheumatic fever patients who have been closely followed at home. To date a total of 34 patients have had clinical type A beta hemolytic streptococcal sore throats. Twenty-four cases received prompt treatment with penicillin with no recurrence of rheumatic fever developing. Of the 10 patients who did not receive penicillin, 4 had a definite recurrence of rheumatic fever and 1 had a probable recurrence. Thus a recurrence rate of at least 40 per cent and probably of 50 per cent was found in those patients who were not treated with penicillin in contrast to an attack rate of 0 per cent in the treated patients. Although the number of patients is small, these data suggest that early penicillin treatment of hemolytic streptococcal infections in rheumatic fever susceptible individuals may prevent attacks of rheumatic fever. It is hoped that by the spring of 1950 sufficient data will have been obtained to warrant further publication."

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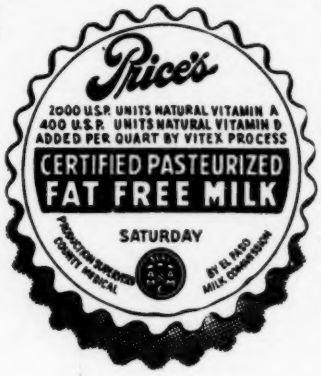

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